Title: The acute effects of the non-nutritive sweeteners aspartame and acesulfame-K in UK diet cola on glycaemic response.

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Running title: Glycaemic effects of sweeteners in diet cola.

Introduction

Prevalence of overweight and obesity has risen considerably in recent decades, doubling worldwide since 1980 (NCD-RisC 2017). In England, figures from the 2016 Health Survey for England (ONS, 2017) show that 61.5% of adults aged 16 and over are overweight or obese. Obesity and consequent illnesses, such as type 2 diabetes mellitus (T2DM) have both high mortality and morbidity (Abdelaal et al. 2017), and place an ever-increasing burden on healthcare systems as a result.

High consumption of sugar-sweetened beverages has been linked to obesity and T2DM (Malik et al. 2010; Greenwood et al. 2014). As a result, it is recommended nationally (SACN 2015) and internationally (WHO 2015) that no more than 5% of daily energy intake be derived from free sugars. Substitution with artificially-sweetened beverages may therefore be of benefit in reducing energy intake leading to potential weight loss according to a 2014 meta-analysis (Miller and Perez 2014).

Non-nutritive sweeteners (NNS), or artificial sweeteners, are sweet-tasting, zero- to low-energy sugar substitutes that may allow reductions in energy intake without reducing food and drink palatability (Burke and Small 2015). NNS frequently used to sweeten beverages include sucralose, aspartame, saccharin and acesulfame-K. In 2017, an estimated 2.3 million people aged 15 and over in the UK consumed artificial sweeteners four times per day or more (Statista 2018).

According to a recent review of the evidence (Raben and Richelsen 2012), the beneficial effects of NNS include the potential for reduced energy intake as well as improved fasting and postprandial glycaemia, insulinaemia and lipidaemia. However, other reviews suggest

potentially adverse metabolic effects of NNS in that consumption may mediate the disruption of normal glucose metabolism and glycaemic homeostasis (Yang 2010; Swithers 2013).

Epidemiological evidence has linked NNS with an increased risk of obesity, metabolic syndrome, and T2DM (Imamura et al. 2015; Azad et al. 2017). However, it is difficult to establish the strength of these associations; studies may or may not adjust for consumption of other foods, and the link between NNS intake and adverse health outcomes may be a result of reverse causality (Mattes and Popkin 2009). Prospective studies indicate that individuals regularly consuming NNS often have a higher baseline BMI than those who forego sweeteners (de Koning et al. 2011). Even when adjusted for baseline BMI, NNS appear to increase risk of obesity and T2DM (Fowler et al. 2008; Bhupathiraju et al. 2013).

Physiological mechanisms linking NNS with obesity are unclear at present (Pereira 2014). The cephalic phase (e.g. gustatory or olfactory signals) of foods prompts innate and learned physiological responses in the gastrointestinal tract in order to optimise digestion and metabolism (Smeets et al. 2010). Regular consumption of low- to no-energy NNS may interfere with normal cephalic phase responses (Mattes and Popkin 2009), reducing the ability of sweet taste to predict energy intake and inducing metabolic dysfunction (Swithers 2013).

Experimentally, some randomised trials have found no additional effect of NNS on glycaemia when co-ingested with glucose (Ma et al. 2010; Wu et al. 2013). However, one study (Pepino et al. 2013) observed an increased glycaemic response to a glucose load following co-ingestion with NNS amongst individuals with obesity. A recent review concluded that consumption of artificial sweeteners had no effect on glycaemia (Nichol et al. 2018). Acesulfame-K, a NNS used with aspartame to sweeten diet cola in the UK, was not included in the review's analysis, but previous work suggests acesulfame-K elevates post-prandial

glycaemia further when co-ingested with a glucose load compared to glucose alone (Bryant et al. 2014). Consumption of NNS has been linked to higher post-prandial glycaemia (Suez et al. 2014). One study comparing NNS with sugar-sweetened beverages (Sørensen et al. 2014) demonstrated an increase in body weight following sucrose supplementation and a decrease following NNS supplementation over ten weeks. Doses used in trials are often in excess of those found in commercially-available beverages and results are thus not necessarily generalisable population-wide.

With the implementation of the 2018 UK Soft Drinks Industry Levy (HMRC 2018) and the consequently increasing cost of sugar-sweetened beverages to consumers, NNS consumption in the UK is likely to increase. This study aims to investigate the glycaemic impact of NNS at levels available in commercial cola products when co-ingested with glucose. As a secondary objective, the glycaemic effects of sugar-sweetened and artificially-sweetened cola will be compared to determine whether or not substitution may confer benefit for glycaemic regulation. To our knowledge, no research into the glycaemic impact of the sweeteners acesulfame-K and aspartame in UK diet cola exists at present. Therefore, this specific combination and its glycaemic impact represents a novel area not yet investigated.

Methods

Sample

A total of ten students and staff volunteered to participate (males *n*=4, females *n*=6, mean age 27.2 ± 6.9 years, mean BMI 23.9 ± 2.4 $kg \cdot m^{-2}$). Sample size was based on methodology in previous primary research and in a seminal review (Brouns et al. 2005). *A priori* analysis revealed that ten participants were sufficient in order to detect an effect size of 0.5 with 80%

power at a two-tailed significance level of 5%. Inclusion criteria included age ≥ 18 years and a BMI between 18 and 30 $kg \cdot m^{-2}$. Exclusion criteria included pregnancy, diabetes, or any individual prescribed glucocorticoids, thyroid medication or gastrointestinal motility enhancers.

All study procedures involving human subjects were approved by the Research Ethics Committee of the Faculty of Science and Engineering at the University of Plymouth. Written informed consent was obtained from each participant prior to the start of the testing procedures.

Study design

A cross-over design was selected on the basis of proposed objectives. Having every participant undergo each 'treatment' controlled for inter-participant differences in metabolism. Each participant attended the laboratory on three separate mornings having fasted from 22:00 the previous evening. Test beverages were matched for fluid and carbohydrate content. Individuals were asked to drink (1) a 25 g glucose (Bulkpowders, Colchester, UK) beverage in 125 mL water + 236 mL water, (2) 25 g glucose drink in 125 mL water with 236 mL diet cola sweetened with aspartame and acesulfame-K (Caffeine-Free Diet Coke, Atlanta, Georgia, USA), and (3) 236 mL sucrose-sweetened, caffeinated cola (Coca Cola, Atlanta, Georgia, USA) with 125 mL water. Test beverages are detailed in Table 1.

Exact quantities of the NNS aspartame and acesulfame-K in UK diet cola are unknown as the information is of a proprietary nature and not currently released by the manufacturer. Blood [glucose] from fingertip capillaries was measured prior to the test (while fasted) and in 15-minute intervals following test drink consumption over a 120-minute period using an Accu-Chek Aviva (Roche, Welwyn Garden City, UK) portable glucometer.

[Table 1 near here]

Data analysis

Glycaemic index of the test drinks was ascertained using the incremental area under the blood glucose curve using methods described previously (Brouns et al. 2005). Individual blood glucose increments > 2 SD outside the mean were discarded. Normality assumptions were satisfied and a one-way repeated measures ANOVA was performed to test for differences in the glycaemic index of each test drink. One-way ANOVAs were also performed at each time point to test for differences in blood glucose response between the three test drinks. Statistical analyses were performed using Minitab Express (Version 1.5.1). All data are reported as mean ± SE.

Results

Postprandial glycaemic responses to the test beverages are depicted in Figure 1. The glucose control and glucose + DC elicited a similar rise in blood glucose above pre-prandial levels. The sucrose-sweetened cola treatment group showed a non-significant lower rise in postprandial glycaemia. All three drinks elicited a decrease in blood glucose below pre-prandial levels after 60 minutes, which persisted for the remainder of the test period.

[Figure 1 near here]

Changes in blood glucose over the test period in response to the three test drinks are displayed in Table 2. A one-way repeated measures ANOVA at each time point showed there were no significant differences in blood glucose change from baseline between the three groups at any of the time points (*P*-values shown).

[Table 2 near here]

The glycaemic index (GI) of the three meals as determined from the incremental area under the curve is detailed in Figure 2. The mean GI for sucrose-sweetened cola (77.0 ± 9.1) was the lowest. The mean GI values of glucose (100.0 ± 15.2) and glucose + DC (104.3 ± 8.5) were similar and a one-way repeated measures ANOVA showed there were no significant differences between the glycaemic response to any of the three test drinks ($F(2,29)=1.68$, $P>0.05$).

[Figure 2 near here]

Discussion

Results showed that there were no significant differences in glycaemic response between any of the test drinks. Compared with a glucose control, co-ingestion of artificially-sweetened diet cola with a glucose drink had no significant effects on postprandial glycaemia. These findings add to the current body of literature demonstrating no effects of NNS on glycaemia (Ma et al. 2010; Tey et al. 2017). These findings have been corroborated by a recent meta-analysis and systematic review that reported no glycaemic impact of NNS (Nichol et al. 2018). However, this review's analysis excluded the NNS acesulfame-K owing to the small number of articles studying its effects and included only those studies investigating the glycaemic impact of NNS in the absence of caloric co-ingestion.

That acute NNS consumption exerted no additional glycaemic influence in the present study may have implications for individuals with obesity or T2DM patients wishing to reduce either sugar intake or dietary GI. However, research indicates that substitution of sugar-sweetened for artificially-sweetened beverages may elicit a compensation effect (Mattes and

Popkin 2009), whereby the reduction in energy consumed results in additional energy consumption later. In the case of aspartame, this compensation effect is lessened when beverages are substituted instead of food (de la Hunty et al. 2006) and is rarely 100% (i.e. an individual seldom consumes 100% of the replaced energy). Substitution of sugar-sweetened beverages for those containing NNS may therefore be beneficial as a means of reducing energy intake and as a subsequent weight loss aid.

Lack of acute glycaemic impact may not prevent NNS consumption from being associated with adverse health consequences in the long term. A recent meta-analysis (Azad *et al.*, 2017) evaluated both randomised controlled trials and prospective cohort studies. The review reported no glycaemic effects of long-term NNS consumption but found that chronic intakes of NNS were associated with increased BMI as well as poor cardiometabolic health including hypertension and cardiovascular events. However, sugar consumption is itself linked to such long-term adverse health effects as metabolic syndrome, T2DM and cardiovascular mortality (Malik et al. 2010; Yang et al. 2014). Substitution of sugar for NNS may therefore still prove beneficial in reducing the risk of poor health outcomes but such associations require further study.

The longer-term glycaemic and metabolic effects of NNS consumption are poorly understood at present. For example, one study suggests consumption of low GI, naturally-sweetened beverages may reduce 24-hour glycaemic profiles (Henry et al. 2009). However, evidence exists that chronic consumption of sweet-tasting, but calorie-free foods/drinks may interfere with innate and learned gastrointestinal hormonal responses, resulting in metabolic derangements (Swithers 2013). Such dysfunction may include poorer postprandial hormonal regulation (a blunted GLP-1 response, for example) and a subsequent weakening of the events leading to satiety. The consumption of NNS alongside a diet high in other sweet-tasting

food/drink (i.e. sugar) may therefore impair the satiety response and increase energy intake (Swithers 2013). Epidemiological evidence has linked NNS consumption with T2DM and other adverse metabolic effects (Imamura et al. 2015; Azad et al. 2017), even after adjustment for adiposity as a confounder. Further research including prospective cohorts and randomised controlled trials is required to determine the long-term metabolic effects arising from chronic NNS consumption.

Differences in sucrose and glucose metabolism may account for the non-significant lower GI of the sucrose-sweetened cola. Though sucrose is digested rapidly, its impact on glycaemia is lower than that of glucose as the fructose component must undergo conversion to glucose (or other substrates) in the liver and thus has a lower GI (Nuttall et al. 2000). In addition, the caffeine present in the sugar-sweetened cola may influence the glycaemic response to carbohydrates. Though some evidence has shown reduced insulin sensitivity (Shi et al. 2016) and increased glycaemia (Moisey et al. 2008) with caffeine ingestion, other studies have found no effects of caffeine on the glycaemic response to food (Aldughpassi and Wolever 2009) or to a glucose drink (Hätönen et al. 2012). Caffeine-free diet cola was selected to minimise influences that might confound the glycaemic effects of the NNS present. Caffeine-free, sugar-sweetened cola is not currently available in the UK and the inclusion of caffeine was necessary. Neither caffeine nor sucrose exerted any significant glycaemic effects in the present study. There were no significant differences between the caffeinated, sucrose-sweetened cola and the glucose control.

One of the potential limitations of this study may include the macronutrient composition of participants' evening meal the previous day (Robertson et al. 2002). For instance, fat-rich, low GI evening meals result in greater glucose tolerance the following morning compared with those of a high GI (Wolever et al. 1988). Moreover, it was assumed that participants

honestly and accurately adhered to instructions concerning pre-test fasting but it is acknowledged that deviations from the protocol may have influenced findings. A further limitation acknowledged is that the inclusion of carbohydrate in all of the test meals may have obscured the effects of NNS. To overcome this, future work might involve measuring the glycaemic response to the NNS aspartame and acesulfame-K in diet cola in the absence of caloric intake. The comparison of the NNS in diet cola with water and a glucose control would allow for observation of the potential independent effects of NNS on glycaemia. The inclusion of only one particular brand of soft drink may limit the generalisability of results. Further research may involve a range of popular artificially sweetened drinks (e.g. lemonade, squash, or sugar-free energy drinks) commonly consumed as substitutions for sugar-sweetened beverages.

Formulations of colas vary between countries in both the sugar-free and sugar-sweetened varieties. For instance, high-fructose corn syrup is used in place of sucrose to sweeten certain brands of cola in the USA. The specific combination of sweeteners in the present study are used to sweeten diet cola in the UK but results may not be transferable to other countries where formulations may differ. The unique combination of aspartame in acesulfame-K in UK diet cola and their potential glycaemic impact represents an area not yet covered. While aspartame and acesulfame-K have been investigated together (Sylvetsky et al. 2016), these NNS were ingested prior to an oral glucose tolerance test. To our knowledge, the present study is the first to investigate the direct glycaemic impact of the sweeteners aspartame and acesulfame-K at commercially available levels in UK cola.

Overall, these results add to the findings demonstrating the glycaemic inactivity of non-nutritive sweeteners. While future research should investigate the long-term glycaemic and metabolic consequences of regular NNS consumption, these observations may have wide-

reaching health implications when viewed in the context of current literature. In a public health context, findings may inform policy in corroborating evidence recommending the substitution of sugar-sweetened drinks for low-energy, artificially-sweetened beverages for obese individuals or those with type 2 diabetes.

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Conflict of Interest

None.

Authorship

L.S. formulated the research question. L.S. and K.R. contributed equally to the study design and analysis. Data collection was undertaken by L.S. The manuscript was drafted by L.S. and edited/amended by K.R and G.R.

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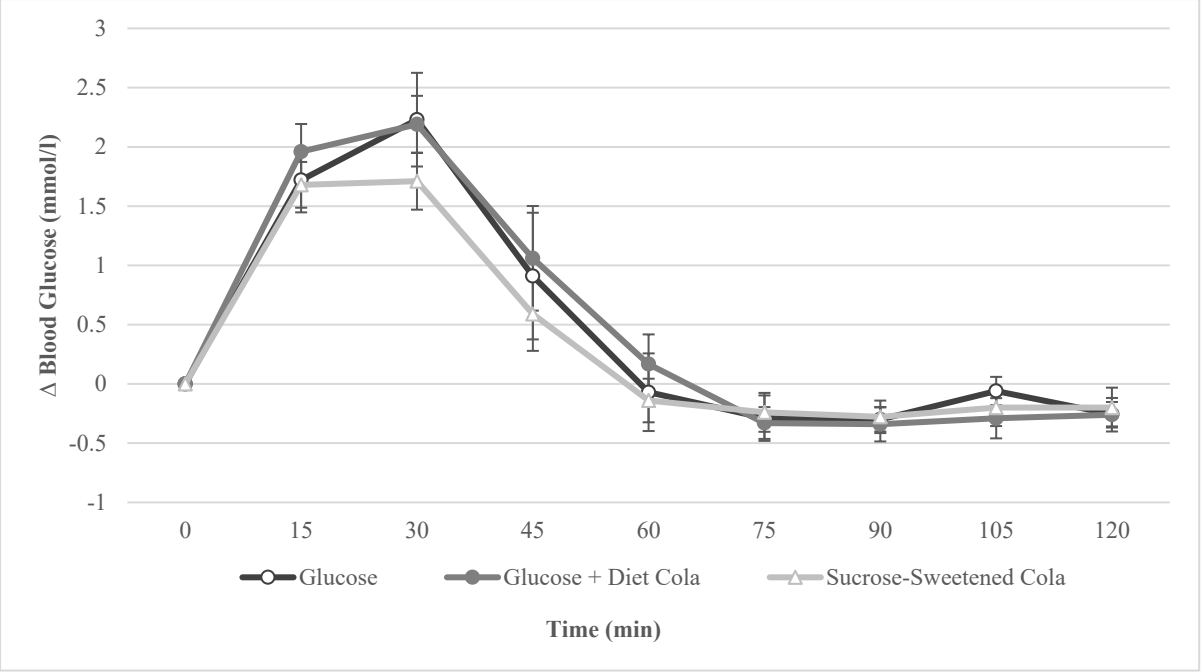

Figure 1. Comparison of the incremental blood glucose values after ingestion of (1) glucose, (2) glucose + caffeine-free diet cola and (3) sucrose-sweetened cola. Values shown as mean increments and error bars denote SEM.

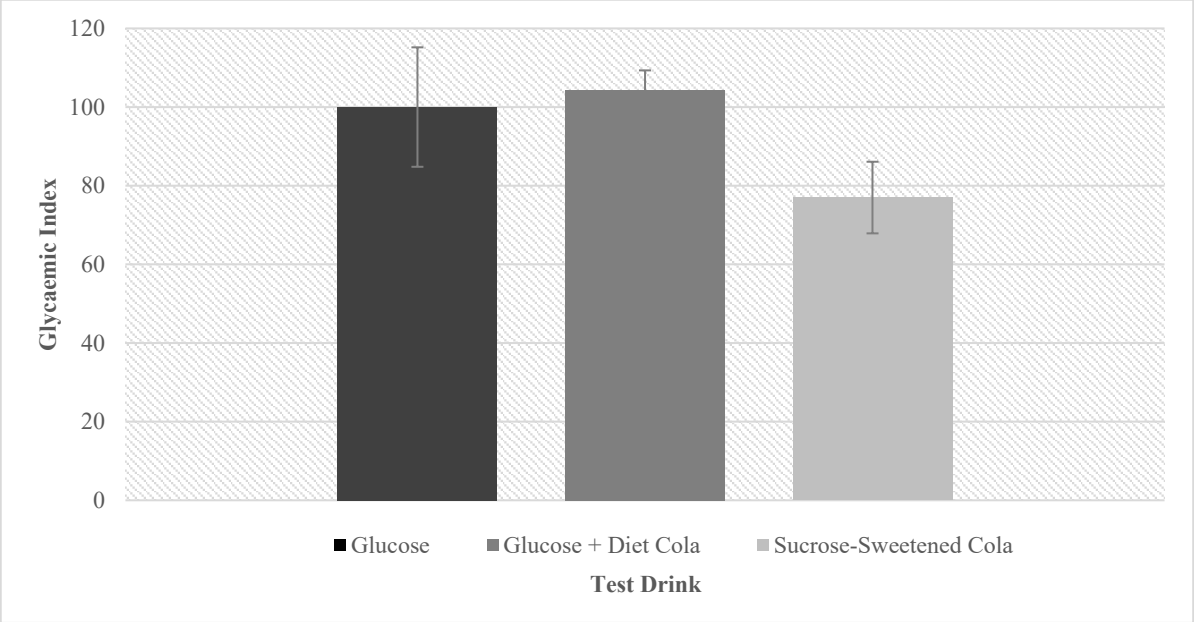

Figure 2. Comparison of glycaemic index (GI) between each test drink. Values shown as mean ± SEM.

Table 1. Test beverages and respective fluid, carbohydrate and caffeine content.

	Beverages consumed	Fluid content (mL)	Carbohydrate content (g)	Caffeine Content (mg)
Test Day 1 (glucose control)	25 g glucose dissolved in 125 mL water + 236 mL water	361	25	0
Test Day 2 (artificially sweetened cola)*	25 g glucose dissolved in 125 mL water + 236 mL caffeine-free diet cola	361	25	0
Test Day 3 (sugar-sweetened cola)	236 mL sucrose-sweetened cola + 125 mL water	361	25	23†

*Sweetened with aspartame and acesulfame-K.
†Caffeine content is approximate. Caffeine-free sugar-sweetened cola is currently unavailable in the UK.

Table 2. Mean blood glucose values over the test period.

Time point (min)	Test drink (Δ blood glucose, mmol/l)			P-value
	Glucose	Artificially sweetened cola	Sugar-sweetened cola	
15	1.72 ± 0.27	1.96 ± 0.23	1.68 ± 0.19	0.66
30	2.23 ± 0.40	2.19 ± 0.24	1.71 ± 0.24	0.43
45	0.91 ± 0.53	1.06 ± 0.44	0.59 ± 0.31	0.74
60	-0.07 ± 0.33	0.17 ± 0.25	-0.14 ± 0.18	0.70
75	-0.29 ± 0.19	-0.33 ± 0.13	-0.24 ± 0.16	0.92
90	-0.30 ± 0.10	-0.34 ± 0.15	-0.28 ± 0.14	0.94
105	0.06 ± 0.12	-0.29 ± 0.17	-0.2 ± 0.16	0.56
120	-0.26 ± 0.10	-0.26 ± 0.14	-0.2 ± 0.17	0.95

Data are presented as means ± SE.